

***Remarks***

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Status of the Claims***

Upon entry of the foregoing amendments, claims 1-2, 9-25, 28, 31-41, 43-56, 58-61, 64-66 and 68-70 are pending in the application, with 1, 53 and 54 being the independent claims. In the Office Action dated December 22, 2003, the Examiner stated that claims 1, 2, 9-25, 28-41, 44-56, 58-61, 64-66 and 68-70 are under consideration. However, Applicants bring to the Examiner's attention that claim 43 is also under consideration.

Claims 29 and 30 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 3-8, 26-27, 42, 57, 62-63 and 67 were previously cancelled.

Claims 1, 2, 11, 12, 14-25, 28, 34-39, 43, 45, 48-56, 59-61, 64-66 and 68-70 have been amended. Support for these amendments can be found throughout the specification as filed. Claims 1, 53 and 54 have been amended to incorporate the language of the previously pending claim 30. No new matter has been introduced by the amendments. Applicants respectfully request entry of these amendments.

***Finality of the Office Action***

In the Office Action dated December 22, 2003, the Examiner stated THIS ACTION IS MADE FINAL, based on Applicants' alleged submission of an information disclosure statement (IDS) under 37 C.F.R. § 1.97(c) and the payment of the fee according to 37 C.F.R. § 1.17(p) on September 26, 2003 under MPEP § 609(B)(2)(i).

A payment of fees according to 37 C.F.R. § 1.17(p) was not submitted on September 26, 2003, as was alleged by the Examiner. Applicants submitted the IDS on September 26, 2003 at the time of filing a Request for Continued Examination. Thus, the IDS of September 26, 2003 was filed under 37 C.F.R. § 1.97(b)(4), not 37 C.F.R. § 1.97(c). An IDS submitted under 37 C.F.R. § 1.97(b)(4) is considered timely and should be considered by the Examiner. An IDS submitted under 37 C.F.R. § 1.97(b)(4) cannot be the basis for a final rejection. See also MPEP § 609(B)(1)(b).

The IDS filed September 26, 2003 cited Ts'o *et al.* (*Adult Urology* 49: 881-885 (1997)). The Examiner alleged that this document "prompted the *new* ground(s) of rejection in this Office action." (Emphasis added.) 37 C.F.R. § 1.113 instructs that final rejections are proper only after a second or subsequent rejection. MPEP § 706.07, first paragraph, states that before a final rejection is in order, a clear issue should be developed between the examiner and applicant. The Examiner's rejection is a *new* rejection based on a newly cited document and is not a second rejection.

Thus, since (1) the IDS was timely filed under 37 C.F.R. § 1.97(b)(4) and (2) the Examiner has raised a new ground for rejection, the finality of the Office Action is improper. Applicants respectfully request that the finality of the Office Action be withdrawn.

***Objections***

Claims 49, 50, 60 and 61 are objected to as allegedly being dependent upon a rejected base claim. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 49 depends from claim 47, which depends from claim 40, which depends from claim 1. Claims 50 depends from claim 47. Claims 60 and 61 depend from claims 1, 53 and 54. Claims 1, 53 and 54 are independent claims. However, in light of the amendments and arguments presented herein, the rejection of claims 1, 40, 53 and 54 is improper. Therefore, Applicants respectfully request reconsideration and withdrawal of the objection to claims 49, 50, 60 and 61.

The Examiner objected to claim 70 due to an informality. Claim 70, section (b) has been amended to recite "probes specific for tumor cell markers." Applicants respectfully request that the objection be withdrawn.

***Rejections Under 35 U.S.C. § 112***

Claims 2, 9, 10, 11, 12, 45, 46 and 51-53 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 2 has been amended to delete reference to "the single cell." Claim 2 has been amended to recite "wherein each probe reacts with a marker of said cells."

Claim 56 has been amended to recite "wherein said isolated cells are further isolated by a negative selection process."

"Probe" has been amended to "probes" in claim 11.

"Cell" has been amended to "cells" in claim 45.

"Marker" has been amended to "markers" in claim 51.

"A single circulating epithelial cancer cell preparation" has been amended to "single circulating epithelial cancer cells" in claim 53.

"Said single cell" in claim 55 has been amended to "said epithelial cancer cells."

"Single circulating epithelial cancer cell" in claim 53 has been amended to "single circulating epithelial cancer cells."

In view of the above amendments, it is respectfully requested that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

***Rejections Under 35 U.S.C. § 102***

Claims 1, 2, 9, 10, 11, 12, 33-41, 43-46, 51, 53-56, 59, 64, 65, 66, 68, 69 and 70 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ts'o *et al.* (*Urology* 49:881-885 (1997)). Applicants respectfully traverse.

A claimed invention is anticipated under 35 U.S.C. §102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), citing *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

Independent claims 1, 53 and 54, as amended, are directed to *concurrently* measuring multiple cellular markers using fluorescent probes, wherein "said fluorescent probes comprise five fluorescent probes." "Concurrent" is defined in the specification as

the presence or absence of markers for a single cell environment as tested *at the same time* (page 7, second paragraph).

The Examiner alleged that Ts'o discloses the use of five different fluorescent probes concurrently (Office Action, page 6). This is incorrect. Ts'o describes two processes that do not occur concurrently. In the first process, under "Immunofluorescence Staining" (page 882, first column, last paragraph), an anti-PSA monoclonal antibody, a polyclonal anti-PsAP antibody and DAPI were used as probes. In the second process, under "Fluorescent In Situ Hybridization (page 882, second column, second paragraph), DNA probes specific for the centromeric regions of chromosomes 7 and chromosomes 8 were used as probes. Ts'o does not teach the use of five or more probes concurrently. Thus, Ts'o does not teach each and every element of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

***Rejections Under 35 U.S.C. § 103***

**A. The rejection under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ts'o *et al.* in view of Ross must be withdrawn.**

Claims 1, 2, 9-12, 33-41, 43-46, 51, 53-56, 58, 59, 64, 65, 66, 68, 69 and 70 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ts'o *et al.* (*Urology* 49:881-885 (1997)) in view of Ross (U.S. Patent No. 5,674,694). Applicants respectfully traverse.

Claims 1, 53 and 54 are independent claims. Claims 2, 9, 10, 11, 12, 33-41, 43-46, 51, 56 and 58 depend, either directly or indirectly, from claim 1. Claim 55 depends from claim 53. Claims 59-61, 64-66 and 68-70 depend from any one of claims 1, 53 and

54. Claims 1, 53 and 54 are directed to methods of characterizing single circulating epithelial cancer cells using fluorescence microscopy for concurrent measurement of multiple cellular markers using five or more fluorescent probes. To establish a *prima facie* case of obviousness, the cited document(s) must teach or suggest each and every element of the claimed invention. Additionally, there must be some suggestion or motivation, either in the prior art itself or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art or combine the teachings of the prior art in the matter posited by the Examiner. MPEP § 2143.

Applicants submit that the combination of the cited documents does not teach each and every element of the claimed invention. The claims require concurrently measuring multiple cellular markers using five fluorescent probes. "Concurrent" is defined as the presence or absence of markers for a single cell environment as tested at the same time (page 7, second paragraph).

Ts'o is discussed above. Ross discloses characterization of cancer cells from bone marrow and stem cells by isolating the cells by a immunomagnetic or density gradient means followed by immunofluorescence using a probe and a stain. Neither Ts'o nor Ross, taken individually or collectively, disclose concurrently measuring multiple cellular markers using five fluorescent probes. Thus, neither Ts'o nor Ross teach or suggest each and every element of the claimed invention. Likewise, neither Ts'o nor Ross provide any motivation to modify or combine their teachings to concurrently measure multiple cellular markers using five fluorescent probes. Thus, Ts'o and Ross do not provide a motivation to modify or combine their teaching to create the claimed invention. Applicants respectfully submit that the Examiner failed to establish a *prima*

*facie* case of obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection.

**B. The rejection under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ts'o *et al.* in view of the abstract of Dale *et al.*, Schlom, Galbraith *et al.*, and Waggoner *et al.* must be withdrawn.**

Claims 1, 2, 9-25, 28, 33-41, 43-46, 51, 53-56, 58, 59, 64-66 and 68-70 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ts'o *et al.* (*Urology* 49:881-885 (1997)) in view the abstract of Dale *et al.* (*Proc Annu Meet Am Soc Clin Oncol* 14:A108 (1995)), Schlom (In: *Molecular Foundation of Oncology* 95-134 (1991)), Galbraith *et al.* (*Cytometry* 12: 579-596 (1991)) and Waggoner *et al.* (*Human Pathology* 27(5): 494-502 (1996)). Applicants respectfully traverse.

Claims 1, 53 and 54 are independent claims. Claims 2, 9-25, 28, 33-41, 43-46, 51, 56 and 58 depend, either directly or indirectly, from claim 1. Claim 55 depends from claim 53. Claims 59, 64-66 and 68-70 depend from any one of claims 1, 53 and 54. Claims 1, 53 and 54 are directed to methods of characterizing single circulating epithelial cancer cells and require the use of fluorescence microscopy for concurrent measurement of multiple cellular markers using five or more fluorescent probes.

Applicants submit that the combination of the cited documents does not teach each and every element of the claimed invention. The claims of the captioned application require concurrently measuring multiple cellular markers using five fluorescent probes. "Concurrent" is defined as the presence or absence of markers for a single cell environment as tested at the same time (page 7, second paragraph).

Ts'o is discussed above. Dale discloses identification of tumor cells using RT-PCR. Schlom discloses monoclonal antibodies that can be used to detect cellular targets. Galbraith discloses the use of four fluorophores to detect lymphocyte sub-populations. Waggoner discloses the use of four fluorophores to detect lymphocytes. Neither Ts'o, Dale, Schlom, Galbraith nor Waggoner, taken individually or collectively, disclose concurrently measuring multiple cellular markers using five fluorescent probes. Thus, neither Ts'o, Dale, Schlom, Galbraith nor Waggoner teach or suggest each and every element of the claimed invention. Likewise, neither Ts'o, Dale, Schlom, Galbraith or Waggoner provide any motivation to modify or combine their teachings to concurrently measure multiple cellular markers using five fluorescent probes. Thus, Ts'o, Dale, Schlom, Galbraith and Waggoner do not provide a motivation to modify or combine their teaching to create the claimed invention. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

**C. The rejection under 35 U.S.C. § 103(a) allegedly being unpatentable over Ts'o *et al.* in view of Takeda *et al.* must be withdrawn.**

Claims 1, 2, 9, 10, 11, 12, 33-41, 43-46, 51, 53-56, 59, 64, 65, 66, 68, 69 and 70 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Takeda *et al.* (*Cancer* 77:934-940 (1996)). Applicants assume that the Examiner intended to combine Takeda with Ts'o *et al.* (*Urology* 49:881-885 (1997)), since a discussion of Ts'o immediately followed this rejection. It is requested that the Examiner notify Applicants if this assumption is incorrect. Applicants respectfully traverse.

Applicants submit that the combination of the cited documents does not teach each and every element of the claimed invention. The claims of the captioned application require concurrently measuring multiple cellular markers using five fluorescent probes. "Concurrent" is defined as the presence or absence of markers for a single cell environment as tested at the same time (page 7, second paragraph).

Ts'o is discussed above. Takeda discloses immunohistochemical detection of androgen receptors from biopsy samples using an anti-androgen receptor antibody. Neither Ts'o nor Takeda, taken individually or collectively, disclose concurrently measuring multiple cellular markers using five fluorescent probes. Thus, neither Ts'o nor Takeda teach or suggest each and every element of the claimed invention. Likewise, neither Ts'o nor Takeda provide any motivation to modify or combine their teachings to concurrently measure multiple cellular markers using five fluorescent probes. Thus, Ts'o and Takeda do not provide a motivation to modify or combine their teachings to create the claimed invention. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

#### ***Other Matters***

The Examiner acknowledged the Declaration Under 37 C.F.R. § 1.131, filed September 26, 2003. The Declaration was submitted in light of Wang *et al.* (Poster Abstract: *International Symposium on Biology of Prostrate Growth*, National Institutes of Health, Bethesda, MD (March 15-18, 1998). The Examiner alleged that the

Declaration was not found to be acceptable in establishing that the present invention was conceived before March 15, 1998. Applicants respectfully traverse. It is unclear whether the Examiner has maintained her rejection under 35 U.S.C. §102(a) based on Wang *et al.*

Wang is directed to characterizing prostate cancer cells using four probes.

Solely to expedite prosecution of the present application, the claims have been amended to require *concurrently* measuring multiple cellular markers using *five* or more fluorescent probes. Wang does not teach, nor suggest, concurrently measuring multiple cellular markers using five fluorescent probes. Thus Wang does not teach each and every element of the claimed invention.

If the Examiner has maintained her rejection under 35 U.S.C. §102(a) based on Wang *et al.*, Applicants respectfully request reconsideration and withdrawal of the rejection in view of the above.

Applicants reserve their right to further establish that the claimed invention was conceived and/or reduced to practice before March 15, 1998.

### ***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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